

## ORIGINAL ARTICLE

# Use of a risk assessment tool to determine the origin of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Xin Chen<sup>1</sup>  | Fatema Kalyar<sup>1</sup> | Abrar Ahmad Chughtai<sup>2</sup> | Chandini Raina MacIntyre<sup>1,3</sup>

<sup>1</sup>Biosecurity Program, The Kirby Institute, Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia

<sup>2</sup>School of Population Health, Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia

<sup>3</sup>College of Public Service & Community Solutions, Arizona State University, Tempe, Arizona, USA

## Correspondence

Xin Chen, Biosecurity Program, The Kirby Institute, Faculty of Medicine, University of New South Wales, Sydney, NSW 2052, Australia.  
Email: [xinjessiechen@protonmail.com](mailto:xinjessiechen@protonmail.com)

## Funding information

Balvi Filantropik Fund; Medical Research Future Fund (MRFF) Research Grant, Grant/Award Number: RFRHPI000280; National Health and Medical Research Council (NHMRC) Investigator Grant, Grant/Award Number: 2016907

## Abstract

The origin of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is contentious. Most studies have focused on a zoonotic origin, but definitive evidence such as an intermediary animal host is lacking. We used an established risk analysis tool for differentiating natural and unnatural epidemics, the modified Grunow–Finke assessment tool (mGFT) to study the origin of SARS-CoV-2. The mGFT scores 11 criteria to provide a likelihood of natural or unnatural origin. Using published literature and publicly available sources of information, we applied the mGFT to the origin of SARS-CoV-2. The mGFT scored 41/60 points (68%), with high inter-rater reliability (100%), indicating a greater likelihood of an unnatural than natural origin of SARS-CoV-2. This risk assessment cannot prove the origin of SARS-CoV-2 but shows that the possibility of a laboratory origin cannot be easily dismissed.

## KEYWORDS

COVID-19, origin, pandemic, risk analysis, SARS-CoV-2

## 1 | INTRODUCTION

Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged from Wuhan, China, in December 2019, there has been ongoing debate around the origins of the virus. There have been two hypotheses of the origin of virus—natural emergence from an animal source and unnatural origin from a laboratory. A wide range of animal species, including bats, are suspected to be the potential reservoirs of SARS-CoV-2 (Andersen et al., 2020), but no animal has yet been identified as the natural or intermediary host of the virus. An article published in March 2020 argued that SARS-CoV-2 had a zoonotic origin (Andersen et al., 2020). Others argue that the presence of a furin cleavage site at the S1/S2 junction, which does not occur in other viruses of the sarbecovirus lineage and which is important for transmission, is unusual (Chretien & Cutlip, 2020; Peacock et al., 2021; Whittaker, 2021). In addition, one of the closest known bat coronaviruses, RaTG13, was being studied at the Wuhan Institute

of Virology (WIV) and has 96.1% homology with SARS-CoV-2 (Jiang & Shi, 2020). The existence and sequence of this virus were not known until after the COVID-19 pandemic began. To date, much of the focus of the debate has been on the phylogenetics of the virus. Limited epidemiologic analysis has focused on the Huanan seafood market, which was a site of the first recognized cluster of cases in December 2019 (Worobey et al., 2022). Several of the first cases, however, did not visit the Huanan markets (Li et al., 2020). In addition, there was serological evidence of SARS-CoV-2 spreading in the United States (US) and Europe in December and November 2019, respectively, which points to an earlier origin of the pandemic than speculated around wet market theories (Althoff et al., 2022; Carrat et al., 2021). The World Health Organization (WHO) conducted two investigations around the origin and released reports on March 26, 2020 (WHO, 2020a) and March 30, 2021 (WHO, 2021), which have concluded the likelihood of four origins: (1) zoonotic introduction (possible to likely), (2) through an intermediary

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2024 The Authors. *Risk Analysis* published by Wiley Periodicals LLC on behalf of Society for Risk Analysis.

host (likely to very likely), (3) via the cold chain products (possible), and (4) laboratory incident (extremely unlikely).

A range of epidemiologic tools are available to analyze the origins of epidemics, with the most commonly used being the Grunow–Finke tool (GFT) (Grunow & Finke, 2002), yet none of these tools have been applied to the study of the origin of SARS-CoV-2 (Chen et al., 2017, 2019). The GFT uses a series of criteria and an algorithm developed for risk scoring to provide comprehensive insight into the origin of epidemics and a likelihood of natural or unnatural origin.

We previously showed the GFT has low sensitivity in correctly identifying unnatural epidemics (Chen et al., 2017). A modified version of the GFT modified Grunow–Finke assessment tool (mGFT) was then developed to improve the sensitivity of prediction by testing and training it against historical outbreaks (Chen et al., 2019). The mGFT has higher sensitivity and specificity in differentiating unnatural from natural epidemics (Chen et al., 2019). In this study, we used mGFT to gain further insight into the origin of SARS-CoV-2.

## 2 | MATERIALS AND METHODS

### 2.1 | Application of mGFT

The mGFT was originally designed to differentiate between natural epidemics and deliberate biological attacks (Chen et al., 2019). In this case, we considered evidence for a natural or unnatural origin of SARS-CoV-2, with a focus on laboratory accidents or leaks as a source of potential unnatural origin. The mGFT contains 11 criteria: *biorisk, unusual strain, geographic distribution, environmental concentration, epidemic intensity, transmission mode, time, unusually rapid spread, population limitation, clinical, and special insights* (Table 1). Each criterion is assigned a value between 0 and 3 points (0 point: no data; 1 point: uncertain; 2 points: obvious peculiarities; 3 points: clear indication or proof), according to the available evidence collected from literature and available data sources, then multiplied by a weighting factor on a scale of 1–3 points as previously described (Chen et al., 2019). The final score provides a likelihood of the outbreak being natural (<30 points) or unnatural (≥30 points).

### 2.2 | Data collection

For this study, we collected data retrospectively on SARS-CoV-2 by country from January 1, 2020 to October 31, 2022, including the number of cases and deaths and incidence. We reviewed retrospective data on SARS-CoV-2 and analyzed the features of the pandemic based on the required criteria for the mGFT to calculate risk scores. Case data was sourced from Our World in Data (Roser et al., 2020), which collates data from multiple sources, including the WHO, the European Center of Disease Control, the John Hopkins University, and official government reports. In addition, information from peer-reviewed publications and gray literature was used to inform the mGFT scoring, as described below.

### 2.3 | Data analysis

Scores were summed for the 11 criteria, with weighting factors applied as per the mGFT (Chen et al., 2019). The sum of assessment points is divided by the maximum points (60 points). The final score is interpreted as follows: <50% (<30/60) favors a natural origin, and ≥50% (≥30/60) favors an unnatural outbreak.

To minimize subjectivity, each criterion was scored independently by two researchers (XC and FK), and then reviewed by two experts (ACC and CRM). Discrepancies among four researchers were discussed until the final scoring was determined. The inter-rater reliability (IRR) (Glen, 2023) was measured for the level of agreement among four researchers. To compare all possible combinations (pairs) for each scoring, we put “0” for disagreement, and “1” for agreement, then summed up all “0”s and “1”s of all 11 criteria, and calculated the average percentage of agreement among raters using the following equation:

$$\text{IRR} = \frac{\text{number of "1"}}{\text{number of criteria} \times \text{number of raters}} \times 100\%.$$

IRR above 75% was considered an acceptable agreement level (Glen, 2023).

## 3 | RESULTS

### 3.1 | Risk assessment criteria and rationale

#### 3.1.1 | Criterion 1: existence of a biological risk

The pneumonia cases caused by SARS-CoV-2 in Wuhan, China were first reported to the WHO on December 30, 2019 (Bogoch et al., 2020). Some, but not all, of the initial cases were linked to the local wet market (Huanan seafood market), pointing to the possibility that the Huanan seafood market was a source of an amplification event rather than the origin of SARS-CoV-2 (WHO, 2022b). The Huanan seafood market was located only 8 miles away from WIV, a biosafety level 4 (BSL-4) facility conducting several gain-of-function research projects funded by the US (Adil et al., 2021; Committee On Oversight & Accountability, 2023; WHO, 2021). However, coronavirus research appears to have been conducted under BSL-2 and 3 at the WIV (Daszak, 2014). The WIV has been involved in longitudinal molecular surveillance and experiments involving SARS-like coronavirus in bats since 2010 (Latinne et al., 2020), with published articles on the first isolation of live SARS-like coronavirus (bat SL-CoV-WIV1) from bat fecal samples (Ge et al., 2013) and 630 novel coronavirus sequences isolated from bat samples in China (Latinne et al., 2020). Based on the nucleocapsid protein of the SARS-like coronavirus strain, the WIV developed a specific enzyme-linked immunosorbent assay to detect antibody from human samples and conducted serological surveillance on residents who were highly exposed to bat populations in 2015 (Wang et al., 2018). With the

**TABLE 1** Criteria of the modified Grunow–Finke assessment tool (Chen et al., 2019).

| Criteria                                                                 | Interpretation of criterion for origins of SARS-CoV-2                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>1. Existence of a biological risk</b>                                 | A biological risk is considered to be a geopolitical environment from which a biological threat could originate. In this case, biological risk is present in an area where dangerous pathogens are researched, developed, produced, or stored and could be released as a result of poor laboratory security or if the laboratory itself is damaged or destroyed. Or any laboratory conducting relevant research is present within 10 mi of the outbreak |
| <b>2. Unusual strain</b>                                                 | The strains may be atypical, rare, antiquated, new emerging, with mutations or signatures of gain-of-function, genetic engineering, or synthetic biology. It may demonstrate increased virulence, unusual environmental stability, resistance to prophylactic and therapeutic measures, or adaptation to humans for easy person-to-person transmission                                                                                                  |
| <b>3. Peculiarities of the geographic distribution of disease</b>        | It is unusual from an epidemiologic perspective, if the disease is identified in a region for the first time ever or re-emerges after a long period of time. For a new pathogen, the location of possible related pathogens from which it may have arisen is compared to the location of emergence                                                                                                                                                      |
| <b>4. High concentration of the biological agent in the environment</b>  | Evidence of unusually high concentrations in the air, soil, and drinking or surface water over a large area or around the area of emergence of the disease                                                                                                                                                                                                                                                                                              |
| <b>5. Peculiarities of the intensity and dynamics of the epidemic</b>    | The intensity and dynamics of an epidemic are characterized by the percentage of cases of a disease per unit of time or the total number of cases                                                                                                                                                                                                                                                                                                       |
| <b>6. Peculiarities of the transmission mode of the biological agent</b> | Different pathogens have different modes of infection. In general, natural epidemics will feature paths of transmission that are typical for the pathogen and its natural hosts. Deviations from expected modes of transmission could indicate an unnatural origin                                                                                                                                                                                      |
| <b>7. Peculiarities of the time of the epidemic</b>                      | Epidemics of certain infectious diseases occur in increased numbers during certain seasons, either because they are dependent on the weather or because they occur after certain intervals in time. If the temporal context of an epidemic is not “typical” and an epidemic does not conform with accepted temporal patterns, then it may point to unnatural origin                                                                                     |
| <b>8. Unusually rapid spread of the epidemic</b>                         | The speed at which epidemics spread is determined by the R0, mode of transmission, virulence, and dose of exposure (dose–response relationship) of the pathogen. It also depends on the susceptibility of the exposed population                                                                                                                                                                                                                        |
| <b>9. Limitation of the epidemic to a specific population</b>            | Unnatural epidemics may occur in large heterogeneous population groups or targeted groups who are selected for political, military, religious, cultural, ethnic, or interpersonal reasons                                                                                                                                                                                                                                                               |
| <b>10. Peculiarities of the clinical manifestation</b>                   | Were the clinical manifestations of the disease expected? For example, do the symptoms reflect the dominant mode of transmission, or are there unusual features such as drug or vaccine resistance or unexpected pathology?                                                                                                                                                                                                                             |
| <b>11. Special insights</b>                                              | Suspicious circumstances and other insights identified prior to the outbreak, during the period of outbreak or post-outbreak                                                                                                                                                                                                                                                                                                                            |

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

capacity of animal experiments, sample collection, and sequence isolation at the WIV, the EcoHealth Alliance collaborated with WIV in a research proposal, DEFUSE, submitted to the Defense Advanced Research Projects Agency in 2018, aiming to insert the furin cleavage site into a group of coronaviruses and extend the roadmap of SARS-like viruses with spillover and pandemic potential using infection experiments on bats, mice with bat immune cells, and humanized mice in the lab (EcoHealth Alliance, 2018). One of the closest known bat viruses, RaTG13, which shares 96.1% homology with SARS-CoV-2, was being studied at the WIV, and its existence was only revealed after the pandemic began (WHO, 2021). On December 2, 2019, the Wuhan Center for Disease Control and Prevention (WHCDC) moved to a location 280 m from the wet market (WHO, 2021). The WHCDC was also studying coronaviruses in BSL-2 facilities, and a move may have increased the chance of a laboratory accident (Eban, 2021; Latham & Wilson, 2020). Although it is plausible that SARS-CoV-2 was accidentally leaked from one of the two laboratories in Wuhan, no direct evidence of SARS-CoV-2 resulting from a laboratory leak or gain-

of-function research has been found, but not all requested information, such as laboratory records, was made available to the WHO investigating team (WHO, 2021). Laboratory accidents are common, and it is possible that an accidentally infected worker within the laboratory may have infected others in the community. Taking the information above into consideration (one of the most closely related bat viruses was housed at WIV, there was a proposal to create a SARS-CoV-2-like virus in 2018, and one laboratory was moved to a new location close to the Huanan Seafood market on December 2, 2019), 3 points were allocated to this criterion.

### 3.1.2 | Criterion 2: unusual strain

SARS-CoV-2 is a novel coronavirus that emerged in 2019. The pandemic potential of SARS-CoV-2 can be attributed to a combination of factors, such as its strong binding affinity for human angiotensin-converting enzyme 2 (ACE2), enhanced viral entry favored by both furin and TMPRSS2 proteases (Peacock et al., 2021), and its ability to suppress

the innate immune response in humans, particularly the interferon-mediated pathway (Harrison & Sachs, 2023). Although it is possible that all of these virus features emerged naturally (Harrison & Sachs, 2023), it is worth noting the unique nature of the furin cleavage site in SARS-CoV-2 at the S1/S2 junction, which plays a crucial role in viral entry into human cells, contributes to priming the virus, and is associated with enhanced pathogenicity and transmissibility (Chretien & Cutlip, 2020). The spike protein of SARS-CoV-2 possesses a fully functional polybasic furin cleavage site that is not present in any other naturally occurring sarbecovirus, despite extensive studies on bat sarbecoviruses in Southeast Asia (Crook et al., 2021). In the past, researchers have conducted experiments involving the insertion of a furin cleavage site into viruses, with the first such experiment on SARS published in 2006 (Follis et al., 2006). In addition, *in silico* modeling indicates that the virus is best adapted to humans, rather than to bats, pangolins, or any other animals, which is consistent with gain-of-function research, rather than a spillover event from another species (Piplani et al., 2021).

Initially, scientists predicted that SARS-CoV-2 would be relatively stable compared to influenza virus, in line with what was known about coronaviruses at the time. However, the virus has proven to be highly mutable, with a mutation rate of at least  $1.5\text{--}1.7 \times 10^{-3}$  nucleotide substitutions per site-year (Morales et al., 2021). This rate is around 50% higher than the estimated mutation rate (Morales et al., 2021) and higher than that of MERS-CoV (McLean et al., 2022).

Given the unusual features above, including the virus being most highly adapted to humans and the furin cleavage site, and known past experiments inserting a furin cleavage site into SARS (Follis et al., 2006), 3 points were allocated to this criterion.

### 3.1.3 | Criterion 3: peculiarities of the geographic distribution of disease

SARS-CoV-2 was first discovered in Wuhan, China in late December 2019 and rapidly spread to multiple countries, resulting in the first known pandemic caused by a coronavirus. During the early stage of pandemic, the spread was reported in Wuhan close to two laboratories (WIV and WHCDC) conducting coronavirus research, before spreading globally (Matthew et al., 2021). According to studies that tested pre-pandemic samples, evidence of SARS-CoV-2 was found in various parts of the world earlier than the recognized outbreak in Wuhan, including Italy, France, the US, and Norway (WHO, 2022b). It was unusual to see the worst epidemic impacts in high-income countries, such as the US, Italy, Spain, and the United Kingdom, in early 2020. This may be confounded by improved surveillance, better case ascertainment, increased travel, trade, and tourism, aging populations, and variations in compliance and leadership (Chen et al., 2023; Güllüoğlu, 2021; Teh et al., 2021). Some variants of concern had a narrow geographic distribution—for example,  $\beta$ , which was dominant in only a few countries, including

South Africa and Bangladesh, whereas  $\alpha$  was dominant in the rest of the world (Tegally et al., 2021). Overall, unlike MERS-CoV, which has a narrow distribution of disease in Middle Eastern countries (Chen et al., 2020), SARS-CoV-2 is globally prevalent. As SARS-CoV2 began in proximity to two laboratories, we assessed this criterion as 2 points.

### 3.1.4 | Criterion 4: high concentration of the biological agent in the environment

The Huanan seafood market in Wuhan was suspected to be the source and epicenter of the COVID-19 pandemic in the early period (Worobey et al., 2022), so the evaluation of this criterion was restricted to Wuhan in 2020 (Liu et al., 2023). The environmental investigation of the Huanan seafood market and other markets in Wuhan was conducted by the China CDC from January 1 to March 2 in 2020. A total of 73 of 923 samples from Wuhan markets were positive, including 44 from surfaces of stalls (16 selling cold-chain products, 13 selling aquatic products, 8 selling poultry, 6 selling seafood, and 5 selling livestock, 2 selling vegetables, and 1 selling wildlife products), 24 from drainage channels and sewage wells inside the wet market, and notably, 3 live viruses were found from the ground and wall inside the stalls with confirmed cases. There were three positive samples from sewage wells in the surrounding areas and one positive sample from another market in Wuhan (Liu et al., 2023; WHO, 2021; Worobey et al., 2022). In contrast, no animal samples from Wuhan wet market tested positive for SARS-CoV-2 nucleic acid (Liu et al., 2023; WHO, 2021), which does not support a zoonotic spillover event at the markets. In contrast, there were documented cases of human infection who had visited the market at that time. This supports the positive samples having originated from the infected human cases. The presence of environmental contamination of SARS-CoV-2 in the Wuhan markets contributes 1 point to this criterion.

### 3.1.5 | Criterion 5: peculiarities of the intensity and dynamics of the epidemic

In December 2019, an explosive outbreak of SARS-CoV-2 started in Wuhan, China, with the initially detected 44 human cases (WHO, 2020b) increasing to 44,412 confirmed cases by February 2020 (Zhu et al., 2020). A very narrow clinical case definition of pneumonia at the start, as well as a lack of diagnostic tests, would have excluded moderate, mild, and asymptomatic infections. The original strain identified in Wuhan was controlled by the public health measures implemented at the time, such as lockdowns, isolation, and quarantine, and was not circulating globally by March 2020 (Plante et al., 2021). The variant that caused the most pandemic activity in the world between March and September 2020 was D614G (Frampton et al., 2021). As the first known pandemic due to a coronavirus, COVID-19 has caused more



than 82.9 million cases worldwide in the first year, including at least 1.9 million deaths, and approximately 768.0 million cases as of July 19, 2023 with 7.0 million deaths (Ritchie et al., 2020). The COVID-19 pandemic had a far greater impact than SARS-CoV-1 epidemic in 2003, which resulted in a total of 8110 confirmed cases with 811 deaths (WHO, 2018), and MERS-COV epidemic with 2591 confirmed cases with 894 deaths since 2012 (WHO, 2022a). The Spanish influenza-H1N1 pandemic between 1918 and 1920 resulted in approximately 500 million suspected cases worldwide with an estimated 675,000 deaths in the US (Center for Disease Control and Prevention, 2019). COVID-19 has resulted in more cases and fatalities (1.01 million) in the US, although case ascertainment with widespread testing is greater now than in 1918 (Ritchie et al., 2020). We therefore allocated 2 points to this criterion.

### 3.1.6 | Criterion 6: peculiarities of the transmission mode of the biological agent

To evaluate this criterion, we restricted the analysis to the initial SARS-CoV-2 outbreak in Wuhan.

1. Animal-to-human transmission: There is speculation of zoonotic spillover from the Huanan market in Wuhan (Ji et al., 2020). The genome-sequencing analysis of SARS-CoV-2 indicates a possible zoonotic origin from bats with an intermediate animal host (variously postulated to be pangolins, minks, snakes, and raccoon dogs) (Hernández et al., 2020; Ji et al., 2020; Lam et al., 2020). The phylogeographic analysis of 1218 horseshoe bats captured in Vietnam in 2017, 2021, and 2022 shows the origin of SARS-like coronavirus from Southern Yunnan and South-east Asia countries (Hassanin et al., 2023), more than 1000 km away from Wuhan, which suggests the possibility of viruses being transported to Wuhan. The closest bat coronavirus to SARS-CoV-2 (BANAL-52 with 96.8% homology) was detected in Laos (WHO, 2022b), followed by RaTG13 (96.1% homology), a bat coronavirus from Yunnan being studied at the WIV (Jiang & Shi, 2020). Subsequent to the pandemic becoming established, infection in minks, domestic cats, and other animals has been documented and may be a source of animal-to-human transmission (Crits-Christoph et al., 2023; Jo et al., 2021). However, no animal host has been found to explain an initial zoonotic spillover event, and the samples from animals in Wuhan wet market were negative for SARS-CoV-2 (Liu et al., 2023). Recently, there has been a controversy on a Zenodo report that points to the origin of SARS-CoV-2 from animal species sold at Huanan seafood market (Crits-Christoph et al., 2023). It is stated that in some positive samples from the Huanan seafood market, SARS-CoV-2 was found to co-occur with animal genetic material, likely from the raccoon dog (Crits-Christoph et al., 2023). This Zenodo report used the same sequence data released from the Global Initiative on Sharing Avian

Influenza Data (GISAID), which were generated by China CDC researchers (Liu et al., 2023). However, its conclusion is inconsistent with the official investigation from the China CDC (Liu et al., 2023), which found no evidence of SARS-CoV-2 in raccoon dogs or other animal samples collected from all 18 animal species at the Huanan seafood market (Liu et al., 2023). Unfortunately, the underlying metagenomic sequencing data was not available from the GISAID database (Crits-Christoph et al., 2023), following the debate on whether the China CDC authors' data was "scooped" during the peer-review stage.

2. Human-to-human transmission: Human-to-human transmission is the dominant mode of transmission (Rocklöv et al., 2020). It occurs via the inhalation of contaminated aerosols, but the virus is also present in feces and urine, and on surfaces (National Center for Immunization and Respiratory Diseases (U.S.) Division of Viral Diseases, 2021). SARS-CoV-2 viruses optimally bind to ACE2 receptors on human cells, particularly in lower respiratory tract and gastrointestinal epithelium, then enter into cells favored by furin and TMRPSS2 (Iwata-Yoshikawa et al., 2022). As aerosol transmission has been identified as the dominant mode of transmission (Wiktorczyk-Kapischke et al., 2021), this does not help with identification of the origin.

Given the uncertain transmission routes from animals and the dominant mode of transmission in humans, we assigned 1 point to this criterion.

### 3.1.7 | Criterion 7: peculiarities of the time of the epidemic

SARS-CoV-2 emerged in the winter of 2019 in China, which is a typically conducive season for respiratory viruses. It was also around the Chinese Lunar New Year, when crowds, gatherings, and travel occur frequently. People travel nationally and internationally at this time, to be with family for the most important celebration of the year. Wuhan is a city of 11.1 million population and a major travel hub (WHO, 2021), so an epidemic arising there at a peak travel time would disseminate the infection globally.

In a report obtained by NBC News Verification Unit, there were signals of a major event around the WIV from October 7 and a possible shut down between October 11 and 19, which might indicate a laboratory incident (Anonymous). From November 17, there were increased keywords, such as "SARS," "Fei Dian" (SARS in Chinese), "cough," and "diarrhea," searched on Chinese social media (Anonymous; Winter, 2021). There were also reports of scientists at WIV, including ones who worked on sarbecoviruses, being sick and requiring hospital care in November 2019 (Dilanian, 2021). Additionally, athletes attending the Military World Games in Wuhan in October reported an outbreak of influenza-like illness, and the US team flew to Wuhan from (and then back to) Seattle, which was an early location for the COVID-19

pandemic in the US (Winter, 2021). The WHO investigation acknowledges the World Military Games outbreak in their report but concludes that the illness was not COVID-19. However, they did not present any evidence to support this conclusion. Such evidence could be gathered by testing stored serum collected from athletes between October and December 2019 for antibodies to SARS-CoV-2. There was also evidence of positive serology for SARS-CoV-2 in the US and Europe in December and November, respectively, of 2019, and of severe pneumonia in China in November (Althoff et al., 2022; Carrat et al., 2021; Gianotti et al., 2021; Kpozehouen et al., 2020). By the end of 2019, multiple Italian and French hospitals reported an unusually high frequency of atypical pneumonia. The retrospective scans of patients revealed that characteristic radiological signs of COVID-19 pneumonia and SARS-CoV-2 virus were found in a stored respiratory sample after retrospective PCR tests (Platto et al., 2021). We have assigned 2 points to this criterion in light of the link between the time of emergence and the events described above.

### 3.1.8 | Criterion 8: unusually rapid spread of the epidemic

The rapid spread of SARS-CoV-2 to multiple countries was observed since the first WHO report of pneumonia clusters in Wuhan, China on December 31, 2019. Although Wuhan city was in lockdown from January 23, 2020, the disease had already spread to 25 countries (with 9927 reported cases) within 1 month. This may have been because of asymptomatic and mild cases not being recognized at the time and lack of diagnostic tests. By February 29, it had spread to 63 countries (with 85,325 reported cases). The WHO declared it a pandemic on March 11, by which time it had spread to 115 countries with 125,922 confirmed cases (Ritchie et al., 2020). Italy was the first country affected by the COVID-19 pandemic among western countries, with SARS-CoV-2 circulating as early as September 2019 (WHO, 2022b) and the first case confirmed from a small town in northern Italy on February 21, 2020. Soon after, the sudden surge of cases made it become the second hardest hit country in the world (Paolini et al., 2020). The explosive spread of SARS-CoV-2 also occurred in the US, with New York City being most severely affected by COVID-19 after the first confirmed cases were detected on March 2, 2020 (Ma et al., 2022). Multiple factors amplified the rapid spread, such as the high population density, travel, frequent interaction, the lack of preexisting immunity, and failures in testing in the US. In the initial epidemic in Wuhan, prior to diagnostic tests being available, CT scanning for the typical ground glass appearance in the lungs was used to diagnose COVID-19 (Lin et al., 2020). Compared to SARS-CoV-1 and MERS-CoV outbreaks, SARS-CoV-2 rapidly spread to many countries and caused a pandemic (Abdelrahman et al., 2020). We have assigned 2 points to this criterion.

### 3.1.9 | Criterion 9: limitation of the epidemic to a specific population

In contrast to MERS-CoV, which has been limited mostly to the Arabian Peninsula (Chen et al., 2020), SARS-CoV-2 caused a pandemic. Individuals with comorbidity, of older age, or with other risk factors are most severely affected. SARS-CoV-2 is less severe in children (Iannarella et al., 2020). Overall, considering the widespread incidence of SARS-CoV-2, 0 point was assigned to this criterion.

### 3.1.10 | Criterion 10: peculiarities of the clinical manifestation

The clinical manifestations of SARS-CoV-2 are different to other  $\beta$ -coronaviruses. It has a vascular pathology and is associated with microthrombi and endotheliopathy (Ahamed & Laurence, 2022). It also features an increased risk of stroke, myocardial infarction, pulmonary emboli, diabetes, and a range of neurocognitive disorders (Al-Aly et al., 2021). The most commonly reported acute symptoms include fever, fatigue, and cough (Rabaan et al., 2020). Other relatively common symptoms include myalgia, anosmia, dyspnea, and gastrointestinal symptoms (Kaye et al., 2021). Less common symptoms include neurological abnormalities like ageusia, confusion, seizures, irritability, depression, sleep disturbance, and neurological complications such as encephalitis, delirium and stroke (WHO, 2018). The neuroinvasive potential of SARS-CoV-2 is a known feature of other human coronaviruses (Keyhanian et al., 2021). In contrast to other respiratory infectious diseases, anosmia and dysgeusia are more common among COVID-19 cases (Mutiawati et al., 2021). The cardiovascular pathology is also unique (Akhtar et al., 2023).

Long COVID is also a unique feature of SARS-CoV-2 and affects between 4% and 30% of survivors (Ahamed & Laurence, 2022). It can include disorders of the lungs, heart, brain, immune, and other systems. COVID-19 also results in dysregulation of the cellular immune system, and the effects of this may include an increased risk of other infections (Ahamed & Laurence, 2022). Autopsy studies also show persistence of the virus in many organ systems after the acute infection (Stein et al., 2022).

In view of the cardiovascular, neurocognitive, and viral persistence effects of the virus, we assigned 2 points to this criterion.

### 3.1.11 | Criterion 11: Special insights

Since SARS-CoV-2 emerged in 2019, there have been debates about whether it arose from a laboratory accident in Wuhan, China. A series of unusual actions at the WIV were documented below. In September 2019, control of the lab was handed over from civilian to military command and control,

and a contractor was hired to renovate the ventilation system within the facility (Committee on Oversight and Accountability, 2023). Simultaneously, for reasons unknown, the WIV removed a large virus database containing approximately 20,000 specimens from bats and mice that had previously been accessible to the public (Markson, 2021). It is unclear whether the database included sequences that could be relevant to the origin of SARS-CoV-2 and whether any attempt was made to cover it up.

The first cases of COVID-19 were detected in a city that hosted two labs doing coronavirus research, the WIV and the Wuhan CDC. From October to November in 2019, a report obtained by NBC News (Anonymous) shows that cell phone signals and traffic declined in the area of WIV, pointing to a major event at the WIV laboratory (Anonymous), which suggests the institute was shut down with mass sterilization after an incident (Markson, 2021). Similar intelligence was available during the anthrax lab leak in 1979 in Sverdlovsk, the Union of Soviet Socialist Republics, with road closures and satellite signal intercepts suggesting the lab came under military control (The National Security Archive, 2001).

Additionally, several instances of poor biosecurity procedures were recorded at the WIV. Some scientists did not follow proper protective equipment protocols while handling bats and were bitten by them (Everington, 2021). In early November 2019, some staff members from the institute were hospitalized with COVID-19-like symptoms (Markson, 2021).

A theoretical article published as a pre-print in 2022 showed “a peculiar pattern of unique restriction endonuclease recognition sites allowing efficient dis- and re-assembly of the viral genome characteristic of synthetic viruses” (Brutzel et al., 2023). The authors noted even spacing between the recognition sites in the genome of SARS-COV-2 and postulated that the restriction enzymes BsaI and BsmBI might have been used to assemble the virus. Then, in January 2024, US Right to Know obtained further documents that aligned with the theoretical article, revealing that early drafts of the DEFUSE proposal intended to assemble synthetic coronaviruses in six segments and insert a furin cleavage site at the same site it exists in SARS-COV-2 (Kopp, 2024). The documents also included a budget item for BsmBI, one of the two restriction enzymes postulated in the 2022 theoretical article.

Other evidence that came to light in 2023 under Freedom of Information requests in the US further indicates that virologists who publicly stated that SARS-COV-2 had a natural origin simultaneously privately communicated doubts about this to each other, and discussed the fact that research at WIV could have led to the creation of SARS-COV-2 (Kopp, 2023). It is possible that US funding of some of the research at WIV was a motivation for the public messaging about natural origins to be promoted and the discussion of a lab accident to be suppressed. The events and incidents above suggest a laboratory incident is possible, so we have assigned a score of 3 to this criterion.

### 3.2 | Overall risk scores

Using the modified GFT algorithm (Chen et al., 2019) (Table 2), the result shows a total of 41 points (68%) out of the maximum 60 points, indicating the SARS-CoV-2 is more likely from an unnatural origin. All raters reached a consensus on the scoring with IRR being 100%.

## 4 | DISCUSSION

We used an established risk analysis framework based on the mGFT for differentiating natural and unnatural epidemics, to investigate the origins of the COVID-19 pandemic. Several studies have dismissed a lab accident as unlikely (Alwine et al., 2023; Andersen et al., 2020; Worobey et al., 2022), but our analysis indicates that both theories of origin are equally plausible. A range of different lines of evidence are required, including phylogenetics, epidemiology, seroepidemiology, and intelligence. The gathering of intelligence may include open source, signals or satellite intelligence, political factors, as well as other “detective work” to piece together the complex question of the origin of SARS-COV-2. This would include full records of viruses housed at the relevant laboratories, of experiments conducted, and records of accidents and illness, among staff. The question of origin cannot be answered solely by phylogenetic analysis, as viruses resulting from gain-of-function research using serial passage in an animal model cannot easily be distinguished from naturally emerged ones. Even viruses created by reverse genetics may be difficult to identify.

Definitive proof of a laboratory leak or natural origin may never be obtained, but risk analysis tools such as the mGFT allow a systematic approach to estimating the likelihood of either origin. The debate about the origins of SARS-COV-2 has been focused largely on medical evidence but not on other intelligence, which is key to identifying unnatural epidemics. The large volume of private communications released under Freedom of Information requests also adds further insights (Kopp, 2023), such as the discrepancy between the public and private views of influential virologists.

The epidemiological evidence needs to be broader than simply the Huanan seafood market, and all data, including outlier data, should be examined. This may include detailed epidemiological analysis of scientists who reported becoming sick at WIV as well as athletes who attended the World Military Games in October 2019, and testing of stored sera collected between October and December 2019 in these athletes. It may also include further analysis of data from countries that had evidence of the virus being present earlier than December 2019, such as Italy, France, and Spain (Carrat et al., 2021; Chavarria-Miró et al., 2021).

Laboratory accidents are common (Gillum, Krishnan, & Byers, 2016), and if the pathogen in question is highly contagious, one infected lab worker can set off an epidemic in the community (Blacksell et al., 2023). The fact that

**TABLE 2** Risk assessment of COVID-19 pandemic origin using the modified Grunow–Finke assessment tool (Chen et al., 2019).

| Criteria                          | Assessment points <sup>a</sup> | Weighting factor | Outcome/maximum points    |
|-----------------------------------|--------------------------------|------------------|---------------------------|
| 1. Existence of a biological risk | 3                              | 3                | 9/9                       |
| 2. Unusual strain                 | 3                              | 3                | 9/9                       |
| 3. Geographic distribution        | 2                              | 1                | 2/3                       |
| 4. Environmental concentration    | 1                              | 3                | 3/9                       |
| 5. Epidemic intensity             | 2                              | 1                | 2/3                       |
| 6. Transmission mode              | 1                              | 1                | 1/3                       |
| 7. Time                           | 2                              | 1                | 2/3                       |
| 8. Unusually rapid spread         | 2                              | 1                | 2/3                       |
| 9. Population limitation          | 0                              | 2                | 0/6                       |
| 10. Clinical                      | 2                              | 1                | 2/3                       |
| 11. Special insights              | 3                              | 3                | 9/9                       |
| Total points                      |                                |                  | <b>41/60 (68%)</b>        |
| Likelihood <sup>b</sup>           |                                |                  | <b>Unnatural outbreak</b> |

<sup>a</sup>Assessment of a criterion: 0—no data; 1—uncertain; 2—obvious peculiarities; 3—clear indication or proof of a biological attack.

<sup>b</sup>Classification by the likelihood: <50%—natural outbreak; ≥50%—unnatural outbreak.

the first cluster of cases was in the vicinity of a world-leading coronavirus laboratory known to be experimenting on SARS-like viruses, as well as a second lab that was also working on coronaviruses, cannot be dismissed as irrelevant. Well-known examples of consequential lab-origin epidemics include the accidental leakage of weaponized anthrax at a Soviet bioweapons facility in Sverdlovsk (The National Security Archive, 2001), the 1977 Russian influenza pandemic (Rozo & Gronvall, 2015), and more recently, a substantial leak of aerosolized *Brucella* from a pharmaceutical plant in China in 2019 (Lina, Kunasekaran, & Moa, 2021). A common theme in such accidents has been denial and cover-up. This occurred in the Sverdlovsk accident, which was declared a natural outbreak by the Soviets and also by the US experts—it was only a confession by Boris Yeltsin after the fall of the Soviet Union that revealed the truth about this deadly accident (The National Security Archive, 2001). The 1977 Russian influenza epidemic is now accepted as likely the result of incomplete attenuation of live virus influenza vaccines, but an unnatural origin was denied for almost 30 years (Rozo & Gronvall, 2015).

This study has several limitations that need to be considered. First, the mGFT tool was previously applied to smaller outbreak scenarios (Chen et al., 2019, 2020), and this is the first time it has been applied to a pandemic. Secondly, the tool was originally designed to detect biowarfare, not laboratory leaks or accidents. In this study, the criteria were interpreted to differentiate between natural origins and laboratory leaks. Therefore, this interpretation may require further testing and training of the tool. Additionally, when using this tool in a pandemic, higher scores are usually assigned to the criteria of “epidemic intensity” and “unusual rapid spread,” which can lead to an overall high score and a likely conclusion of unnatural origin. In addition, subjectivity may exist during the scoring process. To minimize the subjectivity, the initial risk assessment was completed by two researchers and reviewed

by another two experts, with IRR measuring the agreement level (Glen, 2023). We achieved agreement with the criteria assessment and final scoring. Nonetheless, we were conservative in our scoring, and the tool provides a risk analysis framework that can be applied to differentiate between natural and unnatural epidemics. The strengths of this study include a more comprehensive analysis of factors ranging from traditional virology, epidemiology, and medical factors to situational and other intelligence.

The American Biological Safety Association catalogs laboratory accidents and shows them to be exceedingly common, usually as a result of human error (Gillum et al., 2016; Rozo & Gronvall, 2015). Unnatural epidemics arising from such accidents do occur (The National Security Archive, 2001), but to identify them, the question of origin must first be asked. It follows that if the question of unnatural origin is never asked, unnatural epidemics will never be identified. In an age of vastly enabled and accessible technology in genetic engineering and synthetic biology, it is increasingly important to investigate the origin of epidemics and to apply risk analysis tools to gathered intelligence (MacIntyre et al., 2017). We can have more control over the prevention of epidemics that arise from human error than those that arise in nature, because safety systems, training, processes, and risk analysis can be used to improve biosafety. In conclusion, an unnatural origin of SARS-COV-2 is plausible, and our application of the mGFT suggests it is equally or more probable than a natural origin, although both remain possible. The mGFT is highly sensitive in distinguishing between natural and unnatural origins (Chen et al., 2019) and should be included in the toolbox of outbreak investigations.

## ACKNOWLEDGMENTS

This research was supported by the Medical Research Future Fund (MRFF) Research Grant (ID RFRHPI000280), Stage 1 from the Australian Government, and by the Balvi



Filantropik Fund. Raina MacIntyre is supported by the National Health and Medical Research Council's (NHMRC) Investigator Grant 2016907. Xin Chen is supported by the Balvi Filantropik Fund.

Open access publishing facilitated by University of New South Wales, as part of the Wiley - University of New South Wales agreement via the Council of Australian University Librarians.

## ORCID

Xin Chen  <https://orcid.org/0000-0002-9905-2307>

## REFERENCES

- Abdelrahman, Z., Li, M., & Wang, X. (2020). Comparative review of SARS-CoV-2, SARS-CoV, MERS-CoV, and influenza a respiratory viruses. *Frontiers in Immunology*, 11, 552909.
- Adil, M. T., Rahman, R., Whitelaw, D., Jain, V., Al-Taani, O., Rashid, F., Munasinghe, A., & Jambulingam, P. (2021). SARS-CoV-2 and the pandemic of COVID-19. *Postgraduate Medical Journal*, 97(1144), 110–116.
- Ahamed, J., & Laurence, J. (2022). Long COVID endotheliopathy: Hypothesized mechanisms and potential therapeutic approaches. *The Journal of Clinical Investigation*, 132(15), e161167.
- Akhtar, Z., Trent, M., Moa, A., Tan, T. C., Fröbert, O., & MacIntyre, C. R. (2023). The impact of COVID-19 and COVID vaccination on cardiovascular outcomes. *European Heart Journal Supplements*, 25, (Suppl\_A), A42–A49.
- Al-Aly, Z., Xie, Y., & Bowe, B. (2021). High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*, 594(7862), 259–264.
- Althoff, K. N., Schlueter, D. J., Anton-Culver, H., Cherry, J., Denny, J. C., Thomsen, I., Karlson, E. W., Havers, F. P., Cicek, M. S., Thibodeau, S. N., Pinto, L. A., Lowy, D., Malin, B. A., Ohno-Machado, L., Williams, C., Goldstein, D., Kouame, A., Ramirez, A., Roman, A., ... Schully, S. D. (2022). Antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in all of us research program participants, 2 January to 18 March 2020. *Clinical Infectious Diseases*, 74(4), 584–590.
- Alwine, J. C., Casadevall, A., Enquist, L. W., Goodrum, F. D., & Imperiale, M. J. (2023). A critical analysis of the evidence for the SARS-CoV-2 origin hypotheses. *Journal of Virology*, 97(4), e00365–23.
- Andersen, K. G., Rambaut, A., Lipkin, W. I., Holmes, E. C., & Garry, R. F. (2020). The proximal origin of SARS-CoV-2. *Nature Medicine*, 26(4), 450–452.
- Anonymous. MACE E-PAI COVID-19 ANALYSIS. <https://s3.documentcloud.org/documents/6884792/MACE-E-PAI-COVID-19-ANALYSIS-Redacted.pdf>
- Blacksell, S. D., Dhawan, S., Kusumoto, M., Le, K. K., Summermatter, K., O'Keefe, J., Kozlovac, J. P., Almuhaire, S. S., Sendow, I., Scheel, C. M., Ahumibe, A., Masuku, Z. M., Bennett, A. M., Kojima, K., Harper, D. R., & Hamilton, K. (2023). Laboratory-acquired infections and pathogen escapes worldwide between 2000 and 2021: A scoping review. *The Lancet Microbe*, 5(2), e194–e202.
- Bogoch, I. I., Watts, A., Thomas-Bachli, A., Huber, C., Kraemer, M. U., & Khan, K. (2020). Pneumonia of unknown aetiology in Wuhan, China: Potential for international spread via commercial air travel. *Journal of Travel Medicine*, 27(2), taaa008. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7107534/pdf/taaa008.pdf>
- Bruttel, V., Washburne, A., & VanDongen, A. (2023). Endonuclease fingerprint indicates a synthetic origin of SARS-CoV-2. *bioRxiv*, (Preprint), 1–18.
- Carrat, F., Figoni, J., Henny, J., Desenclos, J.-C., Kab, S., de Lamballerie, X., & Zins, M. (2021). Evidence of early circulation of SARS-CoV-2 in France: Findings from the population-based “CONSTANCES” cohort. *European Journal of Epidemiology*, 36(2), 219–222.
- Center for Disease Control and Prevention. (2019). 1918 Pandemic (H1N1 virus). CDC. <https://archive.cdc.gov/#/details?url=https://www.cdc.gov/flu/pandemic-resources/1918-pandemic-h1n1.html>
- Chavarria-Miró, G., Anfruns-Estrada, E., Martínez-Velázquez, A., Vázquez-Portero, M., Guix, S., Paraira, M., Galofré, B., Sánchez, G., Pintó, R. M., & Bosch, A. (2021). Time evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in wastewater during the first pandemic wave of COVID-19 in the metropolitan area of Barcelona, Spain. *Applied and Environmental Microbiology*, 87(7), e02750–02720.
- Chen, X., Chughtai, A. A., & MacIntyre, C. R. (2017). A systematic review of risk analysis tools for differentiating unnatural from natural epidemics. *Military Medicine*, 182(11), e1827–e1835.
- Chen, X., Chughtai, A. A., & MacIntyre, C. R. (2019). Recalibration of the Grunow–Finke assessment tool to improve performance in detecting unnatural epidemics. *Risk Analysis*, 39(7), 1465–1475.
- Chen, X., Chughtai, A. A., & MacIntyre, C. R. (2020). Application of a risk analysis tool to Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in Saudi Arabia. *Risk Analysis*, 40(5), 915–925.
- Chen, X., Kunasekaran, M. P., Hutchinson, D., Stone, H., Zhang, T., Agerup, J., Moa, A., & MacIntyre, C. R. (2023). Enhanced EPIRISK tool for rapid epidemic risk analysis. *Public Health*, 224, 159–168.
- Chretien, J. P., & Cutlip, G. (2020). Working paper 26 May 2020: Critical analysis of Andersen et al. The proximal origin of SARS-CoV-2. <https://drasticresearch.files.wordpress.com/2023/05/an-argument-against-natural-covid-19-creation-copy-2.pdf>
- Committee On Oversight and Accountability. (2023). COVID origins hearing wrap up: Facts, science, evidence point to a Wuhan lab leak. Committee On Oversight and Accountability. <https://oversight.house.gov/release/covid-origins-hearing-wrap-up-facts-science-evidence-point-to-a-wuhan-lab-leak%E2%82%AC%80%E2%82%AC/>
- Crits-Christoph, A., Gangavarapu, K., Pekar, J. E., Moshiri, N., Singh, R., Levy, J. I., Goldstein, S. A., Suchard, M. A., Popescu, S., Robertson, D. L., Lemey, P., Wertheim, J. O., Garry, R. F., Rasmussen, A. L., Andersen, K. G., Holmes, E. C., Rambaut, A., Worobey, M., & Débarre, F. (2023). Genetic evidence of susceptible wildlife in SARS-CoV-2 positive samples at the Huanan Wholesale Seafood Market, Wuhan: Analysis and interpretation of data released by the Chinese Center for Disease Control. *Zenodo*, 1–22.
- Crook, J. M., Murphy, I., Carter, D. P., Pullan, S. T., Carroll, M., Vipond, R., Cunningham, A. A., & Bell, D. (2021). Metagenomic identification of a new sarbecovirus from horseshoe bats in Europe. *Scientific Reports*, 11(1), 14723.
- Daszak, P. (2014). Understanding the risk of bat coronavirus emergence grant notice. National Institute of Allergy and Infectious Diseases. <https://www.documentcloud.org/documents/21055989-understanding-risk-bat-coronavirus-emergence-grant-notice>
- Dilanian, K. (2021). U.S. intel report identified 3 Wuhan lab researchers who fell ill in November 2019. NBC NEWS. <https://www.nbcnews.com/health/health-news/u-s-intel-report-identified-3-wuhan-lab-researchers-who-n1268327>
- Eban, K. (2021). The lab-leak theory: Inside the fight to uncover COVID-19's origins. Vanity Fair. <https://www.vanityfair.com/news/2021/06/the-lab-leak-theory-inside-the-fight-to-uncover-covid-19s-origins>
- EcoHealth Alliance. (2018). Project DEFUSE: Defusing the threat of bat-borne coronaviruses. EcoHealth Alliance. <https://www.documentcloud.org/documents/21066966-defuse-proposal>
- Everington, K. (2021). Video shows Wuhan lab scientists admit to being bitten by bats. Taiwan News. <https://www.taiwannews.com.tw/en/news/4102619>
- Follis, K. E., York, J., & Nunberg, J. H. (2006). Furin cleavage of the SARS coronavirus spike glycoprotein enhances cell–cell fusion but does not affect virion entry. *Virology*, 350(2), 358–369.
- Frampton, D., Rampling, T., Cross, A., Bailey, H., Heaney, J., Byott, M., Scott, R., Sconza, R., Price, J., Margaritis, M., Bergstrom, M., Spyer, M. J., Miralhes, P. B., Grant, P., Kirk, S., Valerio, C., Mangera, Z., Prabhakar, T., Moreno-Cuesta, J., ... Nastouli, E. (2021). Genomic characteristics and clinical effect of the emergent SARS-CoV-2 B.1.1.7 lineage in London, UK: A whole-genome sequencing and hospital-based cohort study. *The Lancet Infectious Diseases*, 21(9), 1246–1256.
- Ge, X.-Y., Li, J.-L., Yang, X.-L., Chmura, A. A., Zhu, G., Epstein, J. H., Mazet, J. K., Hu, B., Zhang, W., Peng, C., Zhang, Y. J., Luo, C. M., Tan, B., Wang, N., Zhu, Y., Crameri, G., Zhang, S. Y., Wang, L. F.,

- Daszak, P., ... Shi, Z.-L. (2013). Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature*, 503(7477), 535–538.
- Gianotti, R., Barberis, M., Fellegara, G., Galván-Casas, C., & Gianotti, E. (2021). COVID-19-related dermatosis in November 2019: Could this case be Italy's patient zero? *British Journal of Dermatology*, 184(5), 970–971.
- Gillum, D., Krishnan, P., & Byers, K. (2016). A searchable laboratory-acquired infection database. *Applied Biosafety*, 21(4), 203–207.
- Glen, S. (2023). Inter-rater Reliability IRR: Definition, Calculation. Statistics How To. [https://www.statisticshowto.com/inter-rater-reliability/#:~:text=Inter%2Drater%20reliability%20is%20the,complex%20\(e.g.%20Cohen's%20Kappa\)](https://www.statisticshowto.com/inter-rater-reliability/#:~:text=Inter%2Drater%20reliability%20is%20the,complex%20(e.g.%20Cohen's%20Kappa))
- Grunow, R., & Finke, E. J. (2002). A procedure for differentiating between the intentional release of biological warfare agents and natural outbreaks of disease: Its use in analyzing the tularemia outbreak in Kosovo in 1999 and 2000. *Clinical Microbiology and Infection*, 8(8), 510–521.
- Güllüoğlu, T. H. (2021). *How to weather the storm: A comparative case study on populist trajectories to COVID-19 pandemic*. Bilkent University. [https://www.proquest.com/openview/88e64283b83c4a84810d838ab7b7bba6/1?pq-origsite=gscholar&cbl=2026366&diss=y&casa\\_token=Egq5bynv2oAAAAA:HQuCmnEtgExDSXPFFHAXaMQp\\_8c0ZLRwhgCBhs3XGpKwvgFq-0HWUGVPoGV8I5dmKQqMssrQrLc](https://www.proquest.com/openview/88e64283b83c4a84810d838ab7b7bba6/1?pq-origsite=gscholar&cbl=2026366&diss=y&casa_token=Egq5bynv2oAAAAA:HQuCmnEtgExDSXPFFHAXaMQp_8c0ZLRwhgCBhs3XGpKwvgFq-0HWUGVPoGV8I5dmKQqMssrQrLc)
- Harrison, N. L., & Sachs, J. D. (2023). What is a furin cleavage site, why is it important, and how might this have arisen in SARS-CoV-2? *Zenodo*, 1.0, 1–32.
- Hassanin, A., Tu, V., Görföl, T., Ngon, L., Pham, P., Hang, C., & Kemenesi, G. (2023). Phylogeographic evolution of horseshoe bat sarbecoviruses in Vietnam and implications for the origins of SARS-CoV and SARS-CoV-2. *Research Square*, (Preprint), 1–60.
- Hernández, M., Abad, D., Eiros, J. M., & Rodríguez-Lázaro, D. (2020). Are animals a neglected transmission route of SARS-CoV-2? *Pathogens*, 9(6), 480.
- Iannarella, R., Lattanzi, C., Cannata, G., Argentiero, A., Neglia, C., Fainardi, V., & Esposito, S. (2020). Coronavirus infections in children: From SARS and MERS to COVID-19, a narrative review of epidemiological and clinical features. *Acta bio-medica: Atenei Parmensis*, 91(3), e2020032–e2020032.
- Iwata-Yoshikawa, N., Kakizaki, M., Shiwa-Sudo, N., Okura, T., Tahara, M., Fukushima, S., & Takeda, M. (2022). Essential role of TMPRSS2 in SARS-CoV-2 infection in murine airways. *Nature Communications*, 13(1), 6100.
- Ji, W., Wang, W., Zhao, X., Zai, J., & Li, X. (2020). Cross-species transmission of the newly identified coronavirus 2019-nCoV. *Journal of Medical Virology*, 92(4), 433–440.
- Jiang, S., & Shi, Z.-L. (2020). The first disease X is caused by a highly transmissible acute respiratory syndrome coronavirus. *Virologica Sinica*, 35(3), 263–265.
- Jo, W. K., de Oliveira-Filho, E. F., Rasche, A., Greenwood, A. D., Osterrieder, K., & Drexler, J. F. (2021). Potential zoonotic sources of SARS-CoV-2 infections. *Transboundary and Emerging Diseases*, 68(4), 1824–1834.
- Kaye, A. D., Cornett, E. M., Brondeel, K. C., Lerner, Z. I., Knight, H. E., Erwin, A., & Urman, R. D. (2021). Biology of COVID-19 and related viruses: Epidemiology, signs, symptoms, diagnosis, and treatment. *Best Practice & Research Clinical Anaesthesiology*, 35(3), 269–292.
- Keyhanian, K., Umeton, R. P., Mohit, B., Davoudi, V., Hajighasemi, F., & Ghasemi, M. (2021). SARS-CoV-2 and nervous system: From pathogenesis to clinical manifestation. *Journal of Neuroimmunology*, 350, 577436.
- Kopp, E. (2023). Visual timeline: 'Proximal origin'. U.S. Right to Know. <https://usrtk.org/covid-19-origins/visual-timeline-proximal-origin/>
- Kopp, E. (2024). US scientists proposed to make viruses with unique features of SARS-CoV-2 in Wuhan. U.S. Right to Know. <https://usrtk.org/covid-19-origins/scientists-proposed-making-viruses-with-unique-features-of-sars-cov-2-in-wuhan/>
- Kpozehouen, E. B., Chen, X., Zhu, M., & MacIntyre, C. R. (2020). Using open-source intelligence to detect early signals of COVID-19 in China: Descriptive study. *JMIR Public Health and Surveillance*, 6(3), e18939.
- Lam, T. T.-Y., Jia, N., Zhang, Y.-W., Shum, M. H.-H., Jiang, J.-F., Zhu, H.-C., Tong, Y. G., Shi, Y. X., Ni, X. B., Liao, Y. S., Li, W. J., Jiang, B. G., Wei, W., Yuan, T. T., Zheng, K., Cui, X. M., Li, J., Pei, G. Q., Qiang, X., ... Cao, W. C. (2020). Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. *Nature*, 583(7815), 282–285. <https://www.nature.com/articles/s41586-020-2169-0.pdf>
- Latham, J., & Wilson, A. (2020). The case is building that Covid-19 had a lab origin. Independent Science News. Disponible en. Consultado en, 2.
- Latinne, A., Hu, B., Olival, K. J., Zhu, G., Zhang, L., Li, H., Chmura, A. A., Field, H. E., Zambrana-Torrel, C., Epstein, J. H., Li, B., Zhang, W., Wang, L. F., Shi, Z. L., & Daszak, P. (2020). Origin and cross-species transmission of bat coronaviruses in China. *Nature Communications*, 11(1), 4235.
- Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., & Feng, Z. (2020). Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *New England Journal of Medicine*, 382(13), 1199–1207.
- Lin, C., Ding, Y., Xie, B., Sun, Z., Li, X., Chen, Z., & Niu, M. (2020). Asymptomatic novel coronavirus pneumonia patient outside Wuhan: The value of CT images in the course of the disease. *Clinical Imaging*, 63, 7–9.
- Lina, S., Kunasekaran, M., & Moa, A. (2021). Brucellosis Outbreak in China, 2019. *Global Biosecurity*, 3(1), 1–11.
- Liu, W. J., Lei, W., He, X., Liu, P., Wang, Q., Wu, Z., & Lu, J. (2023). Perspectives: Back to science in searching for SARS-CoV-2 Origins. *China CDC Weekly*, 5, 1–3.
- Liu, W. J., Liu, P., Lei, W., Jia, Z., He, X., Shi, W., Tan, Y., Zou, S., Wong, G., Wang, J., Wang, F., Wang, G., Qin, K., Gao, R., Zhang, J., Li, M., Xiao, W., Guo, Y., Xu, Z., ... Wu, G. (2023). Surveillance of SARS-CoV-2 at the Huanan seafood market. *Nature*, 1–26. <https://doi.org/10.1038/s41586-023-06043-2>
- Ma, X., Luo, X.-F., Li, L., Li, Y., & Sun, G.-Q. (2022). The influence of mask use on the spread of COVID-19 during pandemic in New York City. *Results in Physics*, 34, 105224.
- MacIntyre, C. R., Engells, T. E., Scotch, M., Heslop, D. J., Gumel, A. B., Poste, G., & Lim, S. (2017). Converging and emerging threats to health security. *Environment Systems and Decisions*, 38(2), 198–207.
- Markson, S. (2021). Chapter twenty-six: The case for a lab leak. In *What really happened in Wuhan* (pp. 381–392). Harper Collins Publishers.
- Matthew, O. J., Eludoyin, A. O., & Oluwadiya, K. S. (2021). Spatio-temporal variations in COVID-19 in relation to the global climate distribution and fluctuations. *Spatial and Spatio-temporal Epidemiology*, 37, 100417.
- McLean, G., Kamil, J., Lee, B., Moore, P., Schulz, T. F., Muik, A., & Pather, S. (2022). The impact of evolving SARS-CoV-2 mutations and variants on COVID-19 vaccines. *MBio*, 13(2), e02979–02921.
- Morales, A. C., Rice, A. M., Ho, A. T., Mordstein, C., Mühlhausen, S., Watson, S., & Hurst, L. D. (2021). Causes and consequences of purifying selection on SARS-CoV-2. *Genome Biology and Evolution*, 13(10), evab196.
- Mutiawati, E., Fahriani, M., Mamada, S. S., Fajar, J. K., Frediansyah, A., Maliga, H. A., Ilmawan, M., Emran, T. B., Ophinni, Y., Ichsan, I., Musadir, N., Rabaan, A. A., Dhama, K., Syahrul, S., Nainu, F., Harapan, H., & Harapan, H. (2021). Anosmia and dysgeusia in SARS-CoV-2 infection: Incidence and effects on COVID-19 severity and mortality, and the possible pathobiology mechanisms—A systematic review and meta-analysis. *F1000Research*, 10, 40–40.
- National Center for Immunization and Respiratory Diseases (U.S.) Division of Viral Diseases. (2021). Scientific brief: SARS-CoV-2 transmission. CDC. <https://stacks.cdc.gov/view/cdc/10594>
- Paolini, D., Maricchiolo, F., Pacilli, M. G., & Pagliaro, S. (2020). COVID-19 lockdown in Italy: The role of social identification and social and political trust on well-being and distress. *Current Psychology*, 41, 1–8.
- Peacock, T. P., Goldhill, D. H., Zhou, J., Baillon, L., Frise, R., Swann, O. C., Kugathasan, R., Penn, R., Brown, J. C., Sanchez-David, R. Y., Braga, L.,

- Williamson, M. K., Hassard, J. A., Staller, E., Hanley, B., Osborn, M., Giacca, M., Davidson, A. D., Matthews, D. A., ... Barclay, W. S. (2021). The furin cleavage site in the SARS-CoV-2 spike protein is required for transmission in ferrets. *Nature Microbiology*, 6(7), 899–909.
- Piplani, S., Singh, P. K., Winkler, D. A., & Petrovsky, N. (2021). In silico comparison of SARS-CoV-2 spike protein-ACE2 binding affinities across species and implications for virus origin. *Scientific Reports*, 11(1), 13063.
- Plante, J. A., Liu, Y., Liu, J., Xia, H., Johnson, B. A., Lokugamage, K. G., Zhang, X., Muruato, A. E., Zou, J., Fontes-Garfias, C. R., Mirchandani, D., Scharton, D., Bilello, J. P., Ku, Z., An, Z., Kalveram, B., Freiberg, A. N., Menachery, V. D., Xie, X., ... Shi, P. Y. (2021). Spike mutation D614G alters SARS-CoV-2 fitness. *Nature*, 592(7852), 116–121.
- Platto, S., Wang, Y., Zhou, J., & Carafoli, E. (2021). History of the COVID-19 pandemic: Origin, explosion, worldwide spreading. *Biochemical and Biophysical Research Communications*, 538, 14–23.
- Rabaan, A. A., Al-Ahmed, S. H., Haque, S., Sah, R., Tiwari, R., Malik, Y. S., & Rodriguez-Morales, A. J. (2020). SARS-CoV-2, SARS-CoV, and MERS-COV: A comparative overview. *Le Infezioni in Medicina*, 28(2), 174–184.
- Ritchie, H., Mathieu, E., Rod s-Guirao, L., Appel, C., Giattino, C., Ortiz-Ospina, E., & Roser, M. (2020). Coronavirus Pandemic (COVID-19). Our World in Data. <https://ourworldindata.org/coronavirus>
- Rockl v, J., Sj din, H., & Wilder-Smith, A. (2020). COVID-19 outbreak on the Diamond Princess cruise ship: Estimating the epidemic potential and effectiveness of public health countermeasures. *Journal of Travel Medicine*, 27(3), taaa030. <https://doi.org/10.1093/jtm/taaa030>
- Roser, M., Ritchie, H., Ortiz-Ospina, E., & Hasell, J. (2020). Coronavirus pandemic (COVID-19). Our World in Data. <https://ourworldindata.org/coronavirus>
- Rozo, M., & Gronvall, G. K. (2015). The reemergent 1977 H1N1 strain and the gain-of-function debate. *MBio*, 6(4), e01013–01015.
- Stein, S. R., Ramelli, S. C., Grazioli, A., Chung, J.-Y., Singh, M., Yinda, C. K., Winkler, C. W., Sun, J., Dickey, J. M., Ylaya, K., Ko, S. H., Platt, A. P., Burbelo, P. D., Quezado, M., Pittaluga, S., Purcell, M., Munster, V. J., Belinky, F., Ramos-Benitez, M. J., ... Ylaya, K. (2022). SARS-CoV-2 infection and persistence in the human body and brain at autopsy. *Nature*, 612(7941), 758–763.
- Tegally, H., Wilkinson, E., Althaus, C. L., Giovanetti, M., San, J. E., Giandhari, J., Pillay, S., Naidoo, Y., Ramphal, U., Msomi, N., Mlisana, K., Amoako, D. G., Everatt, J., Mohale, T., Nguni, A., Mahlangu, B., Ntuli, N., Khumalo, Z. T., Makatini, Z., ... Msomi, N. (2021). Rapid replacement of the Beta variant by the Delta variant in South Africa. *MedRxiv*, (Preprint), 1–26.
- Teh, J. K., Bradley, D. A., Choock, J. B., Lai, K. H., Ang, W. T., Teo, K. L., & Peh, S.-C. (2021). Multivariate visualization of the global COVID-19 pandemic: A comparison of 161 countries. *PLoS ONE [Electronic Resource]*, 16(5), e0252273.
- The National Security Archive. (2001). Volume V: Anthrax at sverdlovsk, 1979. *US intelligence on the deadliest modern outbreak*. The National Security Archive. <https://nsarchive2.gwu.edu/NSAEBB/NSAEBB61/>
- Wang, N., Li, S.-Y., Yang, X.-L., Huang, H.-M., Zhang, Y.-J., Guo, H., Luo, C. M., Miller, M., Zhu, G., Chmura, A. A., Hagan, E., Zhou, J. H., Zhang, Y. Z., Wang, L. F., Daszak, P., & Shi, Z. L. (2018). Serological evidence of bat SARS-related coronavirus infection in humans, China. *Virologica Sinica*, 33(1), 104–107.
- Whittaker, G. R. (2021). SARS-CoV-2 spike and its adaptable furin cleavage site. *The Lancet Microbe*, 2(10), e488–e489.
- Wiktorczyk-Kapischke, N., Grudlewska-Buda, K., Walecka-Zacharska, E., Kwiecińska-Pir g, J., Radtke, L., Gospodarek-Komkowska, E., & Skowron, K. (2021). SARS-CoV-2 in the environment—Non-droplet spreading routes. *Science of the Total Environment*, 770, 145260.
- Winter, A. E. (2021). The impact of the World Military Games on the COVID-19 pandemic. *Irish Journal of Medical Science*, 190(4), 1653–1654.
- World Health Organisation. (2018). SARS (Severe acute respiratory syndrome). WHO. <http://www.who.int/ith/diseases/sars/en/>
- World Health Organisation. (2020a). Origin of SARS-CoV-2. WHO. [https://apps.who.int/iris/bitstream/handle/10665/332197/WHO-2019-nCoV-FAQ-Virus\\_origin-2020.1-eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/332197/WHO-2019-nCoV-FAQ-Virus_origin-2020.1-eng.pdf)
- World Health Organisation. (2020b). Pneumonia of unknown cause—China. WHO. <https://www.who.int/emergencies/disease-outbreak-news/item/2020-DON229>
- World Health Organisation. (2021). WHO-convened global study of origins of SARS-CoV-2: China part. WHO. [https://www.who.int/docs/default-source/coronaviruse/final-joint-report\\_origins-studies-6-april-2021.pdf?sfvrsn=4f5e5196\\_1&download=true](https://www.who.int/docs/default-source/coronaviruse/final-joint-report_origins-studies-6-april-2021.pdf?sfvrsn=4f5e5196_1&download=true)
- World Health Organisation. (2022a). Middle East respiratory syndrome coronavirus (MERS-CoV)—Qatar. WHO. <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON370#:~:text=Between%2022%20March%20and%203,farm%20in%20Al%20Shaniya%20Doha>
- World Health Organisation. (2022b). Preliminary report for the scientific advisory group for the origins of novel pathogens (SAGO). WHO. <https://www.who.int/publications/m/item/scientific-advisory-group-on-the-origins-of-novel-pathogens-report>
- Worobey, M., Levy, J. I., Malpica Serrano, L., Crits-Christoph, A., Pekar, J. E., Goldstein, S. A., Rasmussen, A. L., Kraemer, M. U. G., Newman, C., Koopmans, M. P. G., Suchard, M. A., Wertheim, J. O., Lemey, P., Robertson, D. L., Garry, R. F., Holmes, E. C., Rambaut, A., & Andersen, K. G. (2022). The Huanan seafood wholesale market in Wuhan was the early epicenter of the COVID-19 pandemic. *Science*, 377(6609), 951–959.
- Zhu, H., Wei, L., & Niu, P. (2020). The novel coronavirus outbreak in Wuhan, China. *Global Health Research and Policy*, 5(1), 6.

**How to cite this article:** Chen, X., Kalyar, F., Chughtai, A. A., & MacIntyre, C. R. (2024). Use of a risk assessment tool to determine the origin of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Risk Analysis*, 1–11. <https://doi.org/10.1111/risa.14291>